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10/586,191	07/14/2006	Hiromitsu Fuse	023312-0127	2427

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,191	FUSE ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16,18,20-31,34 and 35* is/are pending in the application.

4a) Of the above claim(s) *11-14,16,18 and 20-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/06; 4/1/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions/Status

Applicant's election of Group Ia, claims 1-10, 34, and 35, drawn to a medicament comprising a GM3 synthase inhibitor, including an inhibitor of GM3 synthase gene expression such as an antisense polynucleotide, siRNA, or shRNA for prevention/treatment of atherosclerosis, in the reply filed on 4/10/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-14, 16, 18, 20-31, 34, and 35 are pending.

Claims 11-14, 16, 18, and 20-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/26/07 and 4/10/08.

Claims 1-10, 34, and 35 are examined herein.

Claim Objections

Claim 2 is objected to because of a minor informality. A definite or indefinite article---"a" or "the"---would appear to be missing between "of" and "GM3" in the final line.

Claims 5 is similarly objected to because of an awkwardness in wording with regard to "substantially complement to." The phrase "complementary to" is preferable.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The U.S. Court of Appeals Federal Circuit decision in *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 86 USPQ2d 1001 (Fed. Cir. 2008) makes it clear that the protection afforded by 35 USC 121 applies only to divisional applications filed as the result of a restriction requirement.

Claims 1-10, 34, and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 67-72, 76, 80, 82, 88, 90, 92, 94, 98, 100, and 104 of copending Application No. 11/662079. Although the conflicting claims are not identical, they are not method for preventing/treating artherscleroses comprising inhibiting the activity of GM3 synthase having the same or substantially the same amino acid sequence of SEQ ID NO:11. SEQ ID NO:11 is identical to instant SEQ ID NO:1. Furthermore, 35 USC 112, first paragraph, support for the conflicting claims shows that conflicting application teaches that siRNA, shRNA, and antisense polynucleotides may all be used to inhibit GM3 synthase activity as by inhibiting the expression of the GM3 synthase gene represented by SEQ

ID NO:12 therein. SEQ ID NO:12 therein is identical to the polynucleotide encoding instant SEQ ID NO:1.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 7, 9, 10, 34, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to a medicament comprising a GM3 synthase inhibitor, or inhibitior of GM3 synthase expression such as an antisense polynucleotide, siRNA, or shRNA, for the prevention and/or treatment of atherosclerosis.

The "medicament for prevention/treatment of athersclerosis" language requires these claims be evaluated to determine whether the specification teaches how to prevent and/or treat atherosclerosis using the claimed medicament.

However, the Examiner fails to find adequate representations in the specification teaching and/or exemplifying the use of the instant medicament to treat, much less prevent atherosclerosis. While treatment may correspond to any positive, therapeutic effect remedial to atherosclerosis, prevention is an absolute, which has not been shown by any art-recognized model nor substantiated by any statistically significant data.

The specification shows that GM3 synthase is increased in atherosclerotic lesions. The specification suggests, therefore, that GM3 synthase is involved in atherosclerosis. The specification shows that GM3 synthase expression can be reduced in cell culture. However, these studies alone fail to show or establish a connection between GM3 synthase reduction in vivo and the treatment or prevention of a disease such as atherosclerosis in vivo in a subject. Certainly, these data alone fail to provide a connection between the inhibition of polypeptides having

"substantially the same amino acid sequence as that of SEQ ID NO:1" and the treatment or prevention of atherosclerosis. In one instance the specification generally asserts this limitation includes an amino acid sequence having at least about 50% homology to SEQ ID NO:1 (paragraph 26 in the pre-grant pub). There is absolutely no evidence that the inhibition of any protein with this level of homology will provide for the claimed effects.

Furthermore, there is no direction or guidance as to how to administer any particular GM3 synthase inhibitor to a subject to treat, much less prevent atherosclerosis. On the basis of the limited guidance in the specification, one of skill would have to engage in undue experimentation to use an inhibitor in the manner intended and would have no assurance that the reduction of GM3 synthase in vivo would ever lead to the effects now claimed.

Certain claims require inhibition of GM3 synthase expression.

Problems related to the pharmaceutical use of antisense, siRNA, and shRNA nucleic acid were well known in the art at the time of invention. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

> One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph).

While Jen et al. direct their comments to antisense and ribozymes, the general challenges outlined are representative of the gene therapy art in general.

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed medicaments to treat one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

A review of the instant application fails to find exemplary disclosure illustrating the proposed use of the medicaments to treat any organism, mammal, or human subject suffering from atherosclerosis. Examples of in vivo use of the claimed medicaments, working or otherwise, are not provided.

Cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Certainly, there is no evidence to substantiate the assertion that reducing GM3 synthase activity or levels would result in the treatment or prevention of atherosclerosis.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids and protein inhibitors in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed medicaments in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "medicament for prevention/treatment of atherosclerosis" language from the instant claims would overcome this rejection.

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-10, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The issues here are twofold: 1) adequate written description support does not exist in the instant application for the genus of GM3 synthase inhibitors claimed in claims 1, 3, and 4, wherein the term "inhibitor" literally embraces any small or large molecule, organic or inorganic drug, lipid, carbohydrate, nucleic acid, peptide, protein, or antibody; and 2) adequate written description support does not exist in the instant application for the genus of substances, polynucleotide or otherwise, that may inhibit the activity or expression of any polynucleotide encoding a protein that is "substantially the same as" SEQ ID NO:1.

Thus, the lack of written description support stems from the breadth of the claims. For example, in their broadest embodiments the claims include any small molecule drug that inhibits any GM3 synthase or any protein having substantially the same sequence as SEQ ID NO:1.

Adequate written description does not exist in the instant application for all these medicaments. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of methods as now claimed in the instant claims. The substances required for the medicaments are recited in terms of their function only, there is no art-recognized correlation between the structure and function, and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the claimed inventions from a recitation of function.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." (Tronzo v. Biomet Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]). The specification need not, however, describe the claimed invention using the same words as the claims (Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 [Fed. Cir. 2000]).

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the full or partial chemical structure of the encompassed genus of inhibitors.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP 2163 states in part that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying

characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

In the instant case, applicants have not satisfied either of these criteria. That is, the instant application discloses no correlation between the structure of a compound or molecule and its ability to inhibit a GM3 synthase, and does not disclose a sufficient number of species representative of the genus. While the specification adequately describes certain polynucleotide inhibitors such as antisense and shRNAs, by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use such agents, adequate written description does not exist for the virtually unlimited number of other inhibitors and antagonists in the claimed genus. Thus, applicants have not shown possession of the claimed medicaments for treating and preventing atherosclerosis.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

Accordingly, only medicaments comprising antisense, siRNA, and/or shRNAs complementary to a polynucleotide encoding SEQ ID NO:1, such as the polynucleotide consisting of SEQ ID NO:2, meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Cambron et al. (1993) *Biochem. Biophys. Res. Comm.* 193:585-590.

Cambron et al. taught the use of UDP-dialdehyde for inhibiting SAT-1, also known as CMP-N-acetylneuraminic acid:lactosylceramide sialyltransferase, also known as GM3 Synthase.

Absent evidence to the contrary, the compositions and/or formulations comprising UDP-dialdehyde are "medicaments" within the scope of what would reasonably be considered to be a medicament---e.g., a composition suitable for medicinal or pharmaceutical use.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Accordingly, Cambron et al. anticipate each of the instant claims.

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Claims 1-10, 34, and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Khvorova et al. (US 2007/0031844 A1).

Khvorova et al. (US 2007/0031844 A1), entitled "Functional and hyperfunctional siRNA," taught several functional siRNAs, including SEQ ID Nos. 607502, which are complementary to a polynucleotide (such as instant SEQ ID NO:2) that encodes a polypeptide having the same or substantially the same sequence as instant SEQ ID NO:1 (see exemplary alignment below).

At paragraph 225, Khvorova et al. taught that their invention is applicable for silencing a broad range of genes, including but not limited to the roughly 45,000 genes of a human genome, and has particular relevance in cases where those genes are associated with diseases. At paragraph 334, it is said the siRNAs may be used as therapeutic agents. At paragraph 277, it is said the siRNAs can be synthesized within cells as hairpin RNAs from a wide variety of vectors, including adenovirus as well as other traditional expression vectors.

Given that each siRNA, by definition, comprises a sense and antisense strand, and that the strands are held together by standard Watson-Crick base pairing, the disclosure of one strand of the siRNA is a disclosure of each strand of the siRNA.

MPEP 2111.02, Section II, states in part that "If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." "During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the

case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim."

MPEP 2112, Section I, states in part that "'[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

MPEP 2112, Section II, states in part that "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference."

Finally, MPEP 2112, Section III, states in part that "Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 USC 102 and 103, expressed as a 102/103 rejection." "There is nothing inconsistent in concurrent rejections for obviousness under 35 USC 103 and for anticipation under 35 USC 102." *In re Best,* 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 USC 102/103 rejection is appropriate for these types of claims as well as for composition claims."

Accordingly, because the compositions and preparations comprising the siRNAs disclosed by Khvorova et al. for diagnostic, research, and therapeutic purposes meet each and every limitation of the instant claims, and a compound and its properties are inseparable, the siRNAs disclosed by Khvorova et al. would necessarily have the function recited in the instant claims. Burden is shifted to applicant to show otherwise (MPEP 2112).

```
US-10-714-333A-607502
; Sequence 607502, Application US/10714333A
; Publication No. US20070031844A1
; GENERAL INFORMATION:
;  APPLICANT: Dharmacon, Inc.
;  APPLICANT:  Khvorova, Anastasia
;  APPLICANT:  Reynolds, Angela
;  APPLICANT:  Leake, Devin
;  APPLICANT:  Marshall, William
;  APPLICANT:  Soaringe, Stephen
;  TITLE OF INVENTION: Functional and Hyperfunctional siRNA
;  FILE REFERENCE: 13499US
;  CURRENT APPLICATION NUMBER: US/10/714,333A
;  CURRENT FILING DATE:  2003-11-14
;  PRIOR APPLICATION NUMBER: 60/502,050
;  PRIOR FILING DATE: 2003-09-10
;  PRIOR APPLICATION NUMBER: 60/426,137
;  PRIOR FILING DATE: 2002-11-14
;  NUMBER OF SEQ ID NOS: 1591911
;  SOFTWARE: Proprietary
; SEQ ID NO 607502
;   LENGTH: 19
;   TYPE: RNA
;   ORGANISM: Homo sapiens
US-10-714-333A-607502

  Query Match             1.7%;  Score 19;  DB 15;  Length 19;
  Score over Length     100.0%;
  Best Local Similarity   57.9%;  Pred. No. 5.3e+05;
  Matches   11;  Conservative    8;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        581 TGTCTGACCTTGAATATTA 599
              ||:|:|||||:|||:|:|:|
Db          1 UGUCUGACCUUGAAUAUUA 19
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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 34, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saito (US Patent 6,555,371), Kapitonov et al. (US 6,280,989), and Goddard et al. (US 7309769) in view of Tuschl et al. (US 2004/0259247 A1), Vickers et al. (2003) *J. Biol. Chem.* 278:7108-7118, Fosnaugh et al. (US 2003/0143732 A1), and Brummelkamp et al. (2002) *Science* 296:550-553.

The gene encoding mammalian GM3 synthase was well known in the prior art, as evidenced by Saito (see SEQ ID NO:7), Kapitonov et al. (see SEQ ID NO:1), and Goddard et al. (see SEQ ID NO:507). Saito, Kapitonov et al., and Goddard et al. each disclosed polynucleotide

sequences encoding GM3 synthase polypeptides that are the same or substantially the same as instant SEQ ID NO:1. Each taught the biological significance of the GM3 synthase gene, its functions, and relevance to cell growth and differentiation. For example, Saito disclosed polynucleotide SEQ ID NO:7 said to correspond to a GM3 synthase gene, which is identical to instant SEQ ID NO:2 and encodes a protein identical to instant SEQ ID NO:1 (col. 7, lines 25-35). Kapitonov et al. taught SEQ ID NO:1, which encodes a polypeptide substantially identical to instant SEQ ID NO:1, and taught that GM3 synthases have several important biological functions, making them important targets for both research and therapeutic purposes (cols. 2-11). Goddard et al. taught SEQ ID NO:507, encoding a polypeptide, SEQ ID NO:508, 100% identical to instant SEQ ID NO:1. See sequence search results in SCORE.

Saito, Kapitonov et al., and Goddard et al. do not teach short interfering RNAs against GM3 synthase.

However, antisense oligonucleotides, ribozymes, and siRNAs, were well known in the prior art. Methods for making and using each of these types of nucleic acid expression inhibitors for research and therapeutic purposes were well established at the time of invention.

For example, Kapitonov et al. taught the use of antisense oligonucleotides to regulate the expression the gene encoding GM3 synthase. For example, see column 18, lines 25-40, in Kapitonov et al. Tuschl et al. and Vickers et al. taught that siRNAs and antisense oligonucleotides alike may be used to investigate gene function in vitro. Tuschl et al. and Fosnaugh et al. each taught that siRNAs may be used to inhibit gene expression in vitro and in vivo for both research and therapeutic purposes. Methods and materials for making and using pharmaceutical compositions are disclosed in therein. Fosnaugh et al. and Brummelkamp et al.

further taught methods for expressing short interfering RNAs in the form of short hairpin RNAs for sequence-specific inhibitioin of gene expression in vitro and in vivo. See paragraphs 57, 114, 221, and 222 of Fosnaugh et al., for example.

Accordingly, each of the elements of the instant claims were well known in the prior art at the time of invention. It would have been obvious at the time of invention to make and use antisense oligonucleotides and siRNAs against the gene encoding GM3 synthase to investigate GM3 synthase function in vitro and in vivo. It would further have been well within the level of skill of the ordinary artisan to design and use said antisense oligonucleotides and siRNAs in the form of a pharmaceutical compositions for research and therapeutic purposes in an animal in vivo, given the wealth of guidance and direction in the prior art concerning the use of siRNAs and antisense oligonucleotides as research and therapeutic tools. One of skill would have had ample reason to make and use nucleic acid inhibitors directed to GM3 synthase to further investigate GM3 synthase function in vitro and in vivo, particularly as it relates to normal and abnormal cell function in vivo.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
June 17, 2008